

REMARKS

The application has been carefully reviewed in light of the Office action, and amended as necessary to more clearly and particularly describe the subject matter that Applicant regards as the invention.

Prior to this Amendment "D", claims 28-33 and 35-53 were pending in the present application. In this amendment, claims 28, 32, 33, 37, 43, 44 and 48 have been amended and claims 31, 42 and 50 have been canceled. Thus, claims 28-30, 32-33, 35-41, 43-49 and 51-53 are currently pending in the present application.

More specifically with regard to the claim amendments, Applicant has: amended independent claim 28 to include the limitations of claim 31, which previously depended from claim 28 and has now been canceled; amended independent claim 37 to include the limitations of claim 42, which previously ultimately depended from claim 37 and has now been canceled; and amended independent claim 48 to include the definite limitations of claim 50, which previously depended from claim 48 and has now been canceled. Since the amendments involve adding the limitations of dependent claims to their base independent claims and canceling the dependent claims, Applicant submits that the amendments presented herein place the application either in condition for allowance or in better form for appeal and should be entered pursuant to 37 CFR 1.116, which concerns amendments after final action or appeal.

Reconsideration of the present application in its current form is hereby requested.

The Examiner has maintained her rejection of claims 28-33 and 35-50 under 35 U.S.C. §103(a) as being unpatentable over Wolfert et al. (Gene Therapy, 1996)

in view of Hanson et al. (WO 95/25809) and further in view of Wu et al. (WO 93/04701) and Zobel et al. (Antisense Nuc. Acid Drug. Devel). Applicant submits that in making this rejection, the Examiner has failed to establish a prima facie case of obviousness.

As set forth in MPEP §2143, three basic criteria must be met in order to establish a prima facie case of obviousness. The three criteria are as follows:

- (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings;
- (2) there must be a reasonable expectation of success; and
- (3) the prior art reference (or references when combined) must teach or suggest all of the claim limitations.

Applicant submits that the Examiner has failed to meet the foregoing requirements necessary to establish a prima facie case of obviousness.

In rejecting former dependent claim 31 (the limitations of which are now incorporated into independent claim 28), former dependent claims 41 and 42 (the limitations of which are now incorporated into independent claim 37) and former dependent claim 49 and 50 (the limitations of which are now incorporated into independent claim 48), the Examiner relies on a combination of the Wolfert et al. reference, the Hanson et al. reference and the Wu et al. reference. More specifically, the Examiner approximates the foregoing claims by taking a test conjugate of DNA and poly(L)lysine disclosed in the Wolfert et al. reference, replacing the poly(L)lysine with the protamine disclosed in the Hanson et al. reference and replacing the DNA with an oligonucleotide disclosed in the Wu et al. reference. The Examiner's response to Applicant's argument concerning the failure

of the references to show a protein "comprising more than 50 percent by weight of arginine" shows that the Examiner's approximation of former dependent claims 31, 41, 42, 49, 50 (now amended independent claims 28, 37 and 48) requires that only the test conjugate (and not the block copolymer) of the Wolfert et al. reference must be utilized and that the poly(L)lysine and the DNA must be replaced by the protamine of the Hanson et al. reference and the oligonucleotide of the Wu et al. reference without incorporating any other moieties taught by the Hanson et al. and Wu et al. references. As will be shown below, this approximation is unmotivated and, in fact, is contrary to the teachings of the Wolfert et al. reference, the Hanson et al. reference and the Wu et al. reference.

Since , by the Examiner's own admission, the Zobel et al. reference is cited only for showing the alteration of surface charges, it is clear that the Zobel et al. reference is not being used to reject former dependent claims 31, 41, 42, 49, 50 (now amended independent claims 28, 37 and 48) and, thus, will not be discussed with regard to the rejection of these claims.

The Wolfert et al. reference discloses the development of a synthetic linear block copolymer for targeted in vitro delivery of DNA, wherein the copolymer comprises a plurality of polymeric blocks, each of which is designed to meet a specific requirement, such as being capable of efficient target-discrimination and penetrating the target cell membrane to selectively gain access to the nucleus (See page 269, second column). The Wolfert et al. reference discloses that the terminal block of the copolymer has a DNA-associating function designed to bind and condense the expression vector leading to spontaneous oriented assembly with DNA. With regard to this terminal block, the Wolfert et al. reference discloses experiments conducted with conjugates consisting of DNA and poly(L)lysine (which

are cited by the Examiner). From the results of these experiments, the Wolfert et al. reference postulates that conjugates of DNA and low molecular weight poly(L)lysine are better tolerated than those formed with high molecular weight poly(L)lysine (See page 273, first partial paragraph). In closing, the Wolfert et al. reference states: "Having identified a suitable structure for the DNA-condensing terminal block of the proposed block copolymer, we plan now to incorporate potential membrane active agents to develop simple di-block copolymers...." (See page 273, second full paragraph). Thus, in sum, the overall teaching of the Wolfert et al. reference is to provide a conjugate of DNA and a block copolymer having a DNA-condensing terminal block comprising low molecular weight poly(L)lysine.

In rejecting claim 28, the Examiner states (with emphasis added) "Wolfert et al. teaches polyelectrolyte complexes (or particles) *consisting* of polycations (poly-lysine) and nucleic acids....." As set forth above, however, the complexes cited by the Examiner were formed merely for experimental purposes to identify a terminal block for the block copolymer. Thus, the Wolfert et al. reference really teaches a conjugate of a nucleic acid and a block copolymer *comprising* poly(L)lysine. In this regard, the entire teaching of the Wolfert et al. reference needs to be considered and not just isolated experiments, as the Examiner has done. As set forth in MPEP§ 2141.02 (with emphasis added), "A prior art reference must be considered in its entirety, i.e., as a whole, ***including portions that would lead away from the claimed invention***".

With regard to replacing the poly(L)lysine of the Wolfert et al. reference with the protamine of the Hanson et al. reference, the Examiner states "One of ordinary skill in the art would have motivated to use equivalently low molecular weight polycations such as that of arginine for the same reason of decreasing toxicity as per

Wolfert et al." This statement, however, ignores the fact that the Wolfert et al. reference recognizes low molecular weight poly(L)lysine as being a "suitable structure" for the DNA-condensing terminal block. If the Wolfert et al. reference finds low molecular weight poly(L)lysine as being suitable, where is the motivation to replace low molecular weight poly(L)lysine with protamine? There is none. At most, one skilled in the art might try to use protamine, but whether a particular combination might be "obvious to try" is not a legitimate test of patentability. *In re Fine*, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988).

With regard to replacing the DNA of the Wolfert et al. reference, the Examiner states "It would have further been obvious to have included the nucleic acid derivative features of the particles taught by the Wu et. al., as Wu et al. discloses the routine practice of the use of DNA analogues produced by "standard synthetic procedures" (p. 4, line 29) in of adjusting molecular stability for the reaching "target [cells] in effective concentrations" (lines 25-26). Initially, Applicant notes that the passages cited by the Examiner merely disclose that the oligonucleotide in the Wu et al. reference is preferably an antisense oligodeoxynucleotide or an analogue of an oligodeoxynucleotide "sufficiently stable to reach the target in effective concentrations", and that antisense oligodeoxynucleotide can be prepared by standard synthetic procedures. As is manifestly clear, these passages provide no motivation to substitute the oligonucleotide of the Wu et al. reference for the DNA of the Wolfert et al. reference. Other, more pertinent, passages in the Wu et al. reference not only fail to provide motivation to substitute the oligonucleotide of the Wu et al. reference for the DNA of the Wolfert et al. reference, but, in fact teach away from the replacement required to approximate former dependent claims 31, 41, 42, 49, 50 (now amended independent claims 28, 37 and 48).

On page 21, lines 15-31, the Wu et al. reference discloses that oligonucleotides have two common problems: inefficient uptake and lack of cell specificity. The lack of cell specificity is due to the fact that "the longer the DNA sequence, the greater the specificity for target mRNA molecules". The Wu et al. reference discloses that Lemaitre et al. covalently coupled an oligonucleotide to poly(L)lysine, *but that the delivery was not cell-specific*. (In this regard, it should be noted that one of the requirements of the block copolymer of the Wolfert et al. reference is cell specificity). The Wu et al. reference addresses this shortcoming of oligonucleotides by providing the oligonucleotide with a carrier comprising a binding agent specific to the target cell (such as a ligand) and a DNA-binding agent, such as a polycation. Thus, the Wu et al. reference teaches away from a complex that only consists of an oligonucleotide and a polycation, which is required for the Examiner's approximation of former dependent claims 31, 41, 42, 49, 50 (now amended independent claims 28, 37 and 48).

As shown above, in order to approximate former dependent claims 31, 41, 42, 49, 50 (now amended independent claims 28, 37 and 48), the overall teaching of the Wolfert et al. reference (a conjugate of DNA and a block copolymer having a DNA-condensing terminal block comprising low molecular weight poly(L)lysine) must be ignored and only the test conjugate (consisting of DNA and poly(L)lysine) must be considered. Then, there must be an unmotivated replacement of the poly(L)lysine in the test conjugate with the protamine from the Hanson et al. reference and an unmotivated replacement of the DNA in the test conjugate with the oligonucleotide of the Wu et al. reference. In both of these replacements, no other moieties from the Hanson et al. reference or the Wu et al. reference must be introduced into the test conjugate, even though such moieties are expressly taught. For example, both the

Hanson et al. reference and the Wu et al. reference teach the inclusion of a target cell binding moiety to improve cell targeting, which is desired by all of the cited references and which is taught by the Wu et al. reference as being especially important for oligonucleotides due to their poor cell targeting. Such teaching, however, must be ignored to make the approximation advocated by the Examiner.

It is clear that the foregoing approximation of former dependent claims 31, 41, 42, 49, 50 (now amended independent claims 28, 37 and 48) is nothing more than hindsight reconstruction, which is counter to established patent law. The Federal Circuit has stated that "If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be "an illogical and inappropriate process by which to determine patentability." *In re Rouffet*, 149 F.3d 1350, 47 U.S.P.Q.2d 1453 (Fed. Cir. 1998).

Based on the foregoing, Applicant submits that the Examiner has failed to establish a prima facie case of obviousness with regard to the rejection of former dependent claims 31, 41, 42, 49, 50 (now amended independent claims 28, 37 and 48) based on a combination of the Wolfert et al. reference, the Hanson et al. reference, the Wu et al. reference and the Zobel et al. reference.

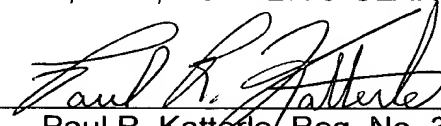
For at least the foregoing reasons, Applicants submit that amended independent claims 28, 37 and 48 are patentable over the Wolfert et al. reference, the Hanson et al. reference, the Wu et al. reference and the Zobel et al. reference (alone or in combination). Applicants consider it apparent that claims 29, 30, 32-33,

35, 36, 38-40, 43-47 and 51-53 are also patentable over the foregoing references because they all depend from claims 28, 37 or 48 and recite additional novel features of the present invention.

In light of the foregoing, it is respectfully submitted that the present application is in a condition for allowance and notice to that effect is hereby requested. If clarification of the amendment or application is desired, or if issues are present which the Examiner believes may be quickly resolved, the Examiner is invited to initiate a telephone interview with the undersigned attorney to expedite prosecution of the present application.

If there are any additional fees resulting from this communication, please charge same to our Deposit Account No. 18-0160, our Order No. WFG-12544.

Respectfully submitted,
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